

Washington International Law Journal

Volume 15 | Number 1

2-1-2006

The Use of Tandem Mass Spectrometry in Newborn Screening: Australia's Experience and Its Implications for United States Policy

Lauren E. Fisher

Follow this and additional works at: <https://digitalcommons.law.uw.edu/wilj>



Part of the [Comparative and Foreign Law Commons](#), and the [Health Law and Policy Commons](#)

Recommended Citation

Lauren E. Fisher, Comment, *The Use of Tandem Mass Spectrometry in Newborn Screening: Australia's Experience and Its Implications for United States Policy*, 15 Pac. Rim L & Pol'y J. 137 (2006).

Available at: <https://digitalcommons.law.uw.edu/wilj/vol15/iss1/6>

This Comment is brought to you for free and open access by the Law Reviews and Journals at UW Law Digital Commons. It has been accepted for inclusion in Washington International Law Journal by an authorized editor of UW Law Digital Commons. For more information, please contact cnyberg@uw.edu.

THE USE OF TANDEM MASS SPECTROMETRY IN NEWBORN SCREENING: AUSTRALIA'S EXPERIENCE AND ITS IMPLICATIONS FOR UNITED STATES POLICY

Lauren E. Fisher[†]

Abstract: In recent years, the United States has drastically increased the number of disorders screened through its newborn screening programs. This increase is made possible by the adoption of new technology, the tandem mass spectrometer ("MS/MS"), which allows screening of up to thirty disorders from a single drop of a newborn's blood. However, such rapid expansion of screening raises concerns regarding the purpose of the screening, as well as the current practices in place for obtaining informed consent. Similar expansion in Australia provides a model of one approach to address these difficult questions. As the first country to begin using MS/MS for newborn screening, the Australian experience sheds light on the implications surrounding such expansion, as well as one method for resolving these issues. However, close analysis reveals that the Australian method for expanding screening would cause dissonance within the U.S. legal system, specifically with regard to informed consent. Therefore, the American states need to re-evaluate the implications of this screening in order to assess whether or not such vast expansion is a good idea. Policy-makers must use caution prior to incorporating any new disorders into newborn screening in order to protect the rights of one of the most vulnerable citizens in our society – the newborn baby.

I. INTRODUCTION

Newborn screening is the most common type of genetic testing practiced in the United States today.¹ These programs are responsible for collection of blood samples, screening, and follow-up for approximately four million births each year.² In the U.S., newborn screening is both run and financed by the states.³ State policy-makers also determine when to screen

[†] The author would like to thank Professor Anna Mastroianni for her guidance and assistance in writing this comment. I truly appreciate your comments. I would also like to thank Professor Kate Batuello for her assistance with research. My editors, Rebecca Jacobs, Katherine Van Maren and Alyssa Vegter, also deserve my thanks for their insightful comments, attention to detail, and patience throughout the entire process. Finally, I must thank my husband Erik for his support through the process of writing this comment, and my son Andrew for being the true inspiration behind the topic.

¹ NORTH CAROLINA CENTER FOR GENOMICS AND PUBLIC HEALTH, GENETIC TESTING, *available at* <http://www.sph.unc.edu/nccgph/phgenetics/testing.htm> (last visited Oct. 30, 2005).

² See Leah Oliver, *Newborn Genetic Screening*, Genetics Brief Issue No. X: National Conference of State Legislatures (2002); U.S. Department of Health and Human Services, 1998 National Newborn Screening Report 16 (2001) [hereinafter National NBS Report].

³ See Linda L. McCabe et al., *Newborn Screening: Rationale for a Comprehensive Fully Integrated Public Health System*, 77 MOLECULAR GENETICS & METABOLISM 267, 269 (2002).

newborns, as well as the types of disorders to include within their screening panel.⁴

One of the more difficult tasks facing states is deciding which disorders to incorporate in the screening panel. A number of governmental and nongovernmental advisory committees developed lists of criteria to allow states to make these decisions in a deliberate and uniform fashion.⁵ However, the degree to which the states rely upon these criteria differs, creating disparity in the number and type of disorders screened among the various states.⁶ As a result, "which side of a state border an infant is born on can make a life-or-death difference."⁷

New technology now allows states to screen for more disorders from a single drop of blood.⁸ More than forty states are already utilizing this new technology – the tandem mass spectrometer ("MS/MS").⁹ The number of disorders included within many states' screening panels has significantly increased due to the adoption of MS/MS.¹⁰ This increase has led to criticism surrounding the inadequacies of MS/MS,¹¹ focusing on the lack of controlled studies regarding treatment, as well as a lack of accurate diagnoses for the disorders now included in screening.¹² The question currently facing policy-

⁴ The term "screening panel" refers to the panel of disorders screened for in any particular state. Including a disorder within the screening panel places a duty upon the state to have the necessary follow-up care in place in the event that a child receives a positive test result. *See id.*

⁵ *See McCabe et al., supra* note 3, at 269.

⁶ According to the National Newborn Screening and Genetics Resource Center, states currently screen for anywhere from 4 to more than 30 disorders. *See* National Newborn Screening and Genetics Resource Center, U.S. NATIONAL SCREENING REPORT (last updated Sept. 22, 2005), *available at* <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf> (last visited Oct. 1, 2005) [hereinafter U.S. NATIONAL SCREENING REPORT].

⁷ Susan Brink, *Rare But Deadly*, U.S. NEWS & WORLD REP., May 30, 2005, *available at* www.usnews.com/usnews/health/articles/050530/30child.htm (last visited Oct. 1, 2005).

⁸ *See McCabe et al., supra* note 3, at 270.

⁹ *See* U.S. National Screening Report, *supra* note 6.

¹⁰ In 1998, the National NBS and Genetics Resource Center reported that the range of disorders included in state newborn screening programs was 4 to 8. Their most recent report indicates that some states are now testing for well over 30 disorders, primarily through MS/MS. *See id.*

¹¹ *See* Susan E. Waisbren et al., *Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress*, 290 JAMA 2564, 2565 (2003) (the "expansion of mandatory screening ... has proceeded despite concerns").

¹² *See* Bridget Wilcken et al., *Screening Newborns for Inborn Errors of Metabolism by Tandem Mass Spectrometry*, 348 NEW ENG. J. MED. 2304, 2304, 2311 (2003) (discussing how use of MS/MS for newborn screening results in identifying patients as having a disorder when in fact they have only a mild, or perhaps benign form that will never result in symptoms. It is not currently possible to determine which of the patients were indeed at risk, and whether treatment decreases decompensation or death after diagnosis because "formal studies are lacking."); *see also* M. J. Thomason et al., *A Systematic Review of Evidence for the Appropriateness of Neonatal Screening Programmes for Inborn Errors of Metabolism*, 20 J. PUB. HEALTH & MED. 331 (1998).

makers is what, if anything, should be done in response to the rapid increase of screening occurring throughout the United States.

Australian newborn screening programs have used MS/MS since 1998.¹³ Their experience has shown that the technology detects more newborns with genetic variances potentially connected to inborn errors of metabolism than were detected under previous screening methods.¹⁴ However, the program also revealed that scientists do not know enough about many of these disorders to accurately predict whether a child with a positive result will actually suffer from that disorder.¹⁵ This lack of knowledge prevented some of the disorders from meeting the criteria used to determine which disorders to include in the Australian states' screening panels.¹⁶ To address this issue, the Australian advisory committee responsible for setting these criteria¹⁷ altered some of the language of their policy recommendations to justify screening for these new disorders within the Australian states.¹⁸

While a simple change in the language of the criteria for screening worked in Australia, a similar change in the United States would violate well-established legal principles, such as personal autonomy and informed consent. Therefore, the American states should examine the rapid addition of disorders to their screening panels by looking at the results of the Australian report.

This Comment argues that the United States should proceed with caution in expansion of its newborn screening programs. Part II analyzes the history of screening in the United States, as well as the criteria traditionally relied upon by state legislators in determining which disorders to include in screening. Part III briefly describes MS/MS, as well as the potential benefits it offers to newborn screening programs. Part IV evaluates the Australian experience utilizing MS/MS, and the implications of the results of that

¹³ See Wilcken et al., *supra* note 12, at 2305.

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ Human Genetics Society of Australia ("HGSA") Policy Statement 1999, HGSA-Royal Australasian College of Physicians ("RACP") Newborn Screening Joint Subcommittee; Newborn Blood-Spot Screening (1999) (copy on file with the Journal) [hereinafter HGSA Policy Statement 1999].

¹⁷ Within Australia, the HGSA and RACP form a joint subcommittee to draft policy statements on issues such as newborn screening. The individual states rely upon these statements when drafting their policies. The criteria developed by the HGSA-RACP for newborn screening assist states in determining which disorders to include in a screening panel. HGSA Policy Statement for Developing New Policies (Sept. 2000), available at <http://www.hgsa.com.au/> (last visited Oct. 1, 2005).

¹⁸ HGSA Policy Statement 2004, HGSA-RACP Newborn Screening Joint Subcommittee; Newborn Blood-Spot Screening (March 18, 2004), available at <http://www.hgsa.com.au/Word/HGSApolicyStatementNewbornScreening0204-18.03.04.doc> (last visited Oct. 1, 2005) [hereinafter HGSA Policy Statement 2004].

program. This section includes a discussion on medium-chain acyl-CoA dehydrogenase deficiency (“MCADD”), focusing on the over-detection of this disorder through MS/MS screening. Part V suggests that because some of the disorders do not meet the criteria required to include them in a screening panel, states should progress with caution prior to the incorporation of more disorders into these panels. This section also includes an evaluation of how Australia’s criteria changed to allow for the addition of these disorders. This Comment concludes with a discussion on how informed consent may prohibit the states from making similar changes to their screening policies. State policy-makers should examine this informed consent issue and re-evaluate their programs before deciding to expand the number of disorders screened. Such analysis will lead them in the future to employ a more cautious approach prior to expanding screening.

II. NEWBORN SCREENING WITHIN THE UNITED STATES MINIMIZES A NEWBORN’S RISK OF MULTIPLE DISORDERS

Newborn screening programs within the United States have evolved to the point where they now successfully minimize a newborn’s risk of developing a number of inborn errors of metabolism. All fifty states and the District of Columbia currently have legislation in place to standardize newborn screening.¹⁹ This legislation typically delegates authority to the state public health department, which oversees the implementation of the program.²⁰ However, this type of screening has not always been available, and is in fact a fairly recent development in healthcare dating back only to the 1960s.²¹

A. *The United States’ Newborn Screening Programs Have Developed to Benefit the Newborn*

In response to the initial test developed to screen for phenylketonuria (“PKU”), the United States has implemented screening programs designed to benefit the health of all newborns. In 1961, microbiologist Robert

¹⁹ See Bradford L. Therrell, Jr., *U.S. Newborn Screening Policy Dilemmas for the Twenty-first Century*, 74 *MOLECULAR GENETICS AND METABOLISM*, 64, 67 (2001). For a list of state legislation see Alissa Johnson, *Newborn Genetic and Metabolic Disease Screening*, NATIONAL COUNCIL OF STATE LEGISLATURES (2005), at <http://www.ncsl.org/programs/health/genetics/newborn.htm> (last visited Oct. 1, 2005).

²⁰ See Ellen Wright Clayton, *Screening and Treatment of Newborns*, 29 *HOUS. L. REV.* 85, 99 (1992).

²¹ See U.S. GEN. ACCOUNTING OFFICE, REPORT TO CONGRESSIONAL REQUESTERS, *Newborn Screening: Characteristics of State Programs*, 4 (2003), available at <http://www.gao.gov/new.items/d03449.pdf> [hereinafter GAO Report] (last visited Oct. 1, 2005).

Guthrie²² invented an inexpensive and simple blood test to screen for the presence of PKU in newborns.²³ PKU occurs when a child has a defect in an enzyme necessary to break down an amino acid present in most foods.²⁴ Without this enzyme, the amino acid collects within the child's blood causing severe mental retardation.²⁵ However, with proper treatment consisting of a special diet containing little to no phenylalanine, a child can avoid most, if not all, of the effects of this disease.²⁶

After watching the effects of PKU on his niece, Guthrie became determined to create a test usable for mass, population-based screening.²⁷ The result of his work was a simple test in which healthcare workers collect a small drop of the newborn's blood on filter paper and then analyze it for the presence of a genetic marker indicating whether the child in question has PKU.²⁸ Guthrie achieved his objective through this test and opened the door for mass screening of PKU in newborns. He then began to promote the passage of state laws mandating PKU screening for all newborns.²⁹

Initially, the medical community resisted accepting PKU testing on newborns.³⁰ Scientists estimate this disorder has an incidence in the United States, Britain, and most of Western Europe between one in 11,000 to 15,000 births,³¹ and the rarity caused hesitation in mandating such wide-spread screening.³² However, Guthrie, along with the National Association for Retarded Citizens, exerted pressure upon the states and eventually succeeded in persuading Massachusetts to institute a large-scale pilot program utilizing

²² Robert Guthrie was a research scientist at Roswell Park Cancer Institute in Buffalo, New York, as well as a faculty member at the University of Buffalo School of Medicine and Biomedical Sciences at the time of this discovery. He later became a professor emeritus of pediatrics and microbiology at the University of Buffalo. Throughout his life, he was also a surgeon with the National Institute of Health and a professor and chair of the Department of Bacteriology and Immunology at the University of Kansas. He retired in 1986 and died in 1995 in Seattle, Washington. *Obituaries: Robert Guthrie, Professor; Developer of PKU Test*, U. BUFFALO REP., Aug. 31, 1995, available at <http://www.buffalo.edu/reporter/vol27/vol27n01/n14.html> (last visited Oct. 1, 2005).

²³ See Robert Guthrie, Blood Screening for Phenylketonuria, 178 JAMA 863 (1961); Robert Guthrie & Ada Susi, A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants, 32 PEDIATRICS 338 (1963).

²⁴ See Diane B. Paul, The Politics of Heredity: Essays on Eugenics, Biomedicine, and the Nature-Nurture Debate 173 (1998).

²⁵ See Donal H. Chace & Theodore A. Kalas, A Biochemical Perspective on the Use of Tandem Mass Spectrometry for Newborn Screening and Clinical Testing, 38 CLINICAL BIOCHEMISTRY 296 (2005).

²⁶ See PAUL, *supra* note 24.

²⁷ See Therrell, *supra* note 19.

²⁸ See GAO Report, *supra* note 21, at 14-15 (2003).

²⁹ See Harvy L. Levy & Simone Albers, *Genetic Screening of Newborns*, 200.01 ANN. REV. GENOMICS HUM. GENETICS 139, 140 (2000); L.B. Andrews, *State Laws and Regulations Governing Newborn Screening*, 1985 CHICAGO: AM. BAR FOUND. 167 (1985).

³⁰ See Therrell, *supra* note 19.

³¹ See PAUL, *supra* note 24.

³² *Id.*

the test on newborns.³³ Finally, in 1963, Massachusetts adopted mandatory testing for PKU on all newborns.³⁴ By the late 1960s, almost every state had mandated PKU testing on all newborns,³⁵ and by 1975, Guthrie's test was mandatory in 43 states,³⁶ covering an estimated 90% of all newborns born in the United States.³⁷

The widespread acceptance of PKU testing in the United States was not an indication that the test was flawless. In fact, much remained unknown about the disease, thus decreasing the reliability of the initial tests.³⁸ Specifically, many questions remained regarding the disease's diagnosis.³⁹ In 1970, a survey indicated that the false-positive rate (those receiving a positive test result that did not actually have the disease) was abnormally high;⁴⁰ for every infant identified who actually had the disease, an estimated nineteen others received false identification from the test.⁴¹ More troubling was the fact that these false diagnoses were not harmless.⁴² The severely restricted diet used to treat children with a PKU diagnosis ironically caused mental retardation, the condition it was designed to prevent, in some of the children who falsely tested positive.⁴³ In 1975, the National Research Council Committee on Inborn Errors of Metabolism issued a statement in which they admitted that "screening was started, frequently under mandatory laws, when questions regarding diagnosis, prognosis, and optimal management were unanswered."⁴⁴ Eventually scientists learned enough about the disorder to reduce the false positive rate to an acceptable level.⁴⁵ However, states could have avoided this problem had the test not been so rapidly adopted.⁴⁶

³³ See American Academy of Pediatrics, *Serving the Family from Birth to the Medical Home*, 106 PEDIATRICS 389, 389-390 (2000) [hereinafter AAP]; PAUL, *supra* note 24, at 174.

³⁴ PAUL, *supra* note 24, at 173.

³⁵ Levy & Albers, *supra* note 29, at 140.

³⁶ See AAP, *supra* note 33.

³⁷ NATIONAL RESEARCH COUNCIL COMMITTEE FOR THE STUDY OF INBORN ERRORS OF METABOLISM, GENETIC SCREENING: PROGRAMS, PRINCIPLES, AND RESEARCH, 23 (National Academy of Sciences: Washington, D.C. 1975).

³⁸ *Id.* at 28.

³⁹ See PAUL, *supra* note 24, at 177.

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² See Clayton, *supra* note 20, at 106; see also Gina Kolata, *Panel to Advise Testing Babies for 29 Diseases*, N.Y. TIMES, February 21, 2005.

⁴³ See Clayton, *supra* note 20, at 105; Kolata, *supra* note 42.

⁴⁴ See Therrell, *supra* note 19, at 69-70 (citing National Research Council Committee for the Study of Inborn Errors of Metabolism, *Genetic Screening: Programs, Principles, and Research* 32 (1975)).

⁴⁵ See Clayton, *supra* note 20, at 106.

⁴⁶ See *id.*; Kolata, *supra* note 42.

Despite its initial problems, the medical community regards the PKU test as a gold standard for population based screening.⁴⁷ Slowly, states began to look at other diseases also appropriate for testing.⁴⁸ As the states widened the scope of their screening, questions arose about how to determine which disorders should be included within a screening panel. Different advisory committees came forward with criteria for determining whether the screening panel should include a particular disorder. These criteria provide structure to the programs⁴⁹ and have greatly impacted newborn screening programs in the United States.⁵⁰

B. The Criteria Developed in the United States to Determine Which Disorders to Include in a Screening Panel Are Necessary to Protect the Best Interests of the Newborn

The criteria developed for newborn screening by advisory committees within the United States are necessary to protect the best interests of the child with regard to newborn screening. Wilson and Junger published the first set of criteria addressing the issue of newborn screening in 1968.⁵¹ Their intention was to assist public health organizations and policy-makers in determining how to bring treatment to those with previously undetected diseases while avoiding harm to those persons not in need of treatment.⁵² By using these criteria, screening would occur only for disorders posing a significant threat to the infant's health where a treatment is available in the event of a positive result.

As screening programs developed, different organizations released their own criteria designed to help identify which disorders a screening panel should include. In 1974, William K. Frankenburg⁵³ addressed this issue and concluded that:⁵⁴

The availability of a suitable screening test does not justify screening for a disease unless the disease is important,

⁴⁷ See PAUL, *supra* note 24, at 176; Kolata, *supra* note 42.

⁴⁸ See Levy & Albers, *supra* note 29, at 139.

⁴⁹ D.A.C. Elliman, C. Dezateux & H.E. Bedford. *Newborn and Childhood Screening Programmes: Criteria, Evidence, and Current Policy*, 87 ARCHIVES DISEASE CHILDHOOD 6 (2002).

⁵⁰ See Therrell, *supra* note 19, at 67.

⁵¹ J.M.G. WILSON & G. JUNGHER, *Principles and Practice of Screening for Disease*, in PUB. HEALTH PAPERS No.34 (Geneva: World Health Organization 1968) [hereinafter WILSON & JUNGHER].

⁵² See *id.* for the criteria developed by Wilson & Junger

⁵³ William K. Frankenburg, MD, MSPH, is Professor Emeritus of Pediatrics and Preventative Medicine at the University of Colorado School of Medicine.

⁵⁴ William Frankenburg, Selection of Diseases and Tests in Pediatric Screening, 54 PEDIATRICS 612 (1974).

relatively prevalent, and amenable to early treatment. . . . Screening which is carried out without knowledge and consideration of these criteria . . . may actually do more harm than good.⁵⁵

In 1975, the National Academy of Sciences also addressed the issue of which disorders to include in newborn screening.⁵⁶ Their criteria focused more on the availability of treatment, including education, follow-up care, and counseling, as well as the public benefit gained from the inclusion of a test within the screening program.⁵⁷ Another relevant change was the addition of informed consent⁵⁸ as a critical aspect of any screening done upon a newborn.⁵⁹

The Institute of Medicine published the next set of criteria in 1994.⁶⁰ These focused on the benefit to the newborn rather than to the general public, as well as the ability to confirm diagnosis and the availability of treatment.⁶¹ The committee also noted that they did not believe “newborns should be screened using multiplex testing for many disorders at one time unless all of the disorders meet the principles described.”⁶²

Finally, in 1999 the Maternal and Child Health Bureau (“MCHB”)⁶³ responded to Congressional interest in newborn screening by providing financial support for the American Academy of Pediatrics (“AAP”) to convene a Newborn Screening Task Force.⁶⁴ In 2000, this Task Force published a report recommending the introduction of new tests in a “carefully designed manner that facilitates evaluation of the risks and benefits of screening, including the efficacy of follow-up and treatment protocols.”⁶⁵

⁵⁵ *Id.*

⁵⁶ See Therrell, *supra* note 19, at 68-69.

⁵⁷ *Id.*

⁵⁸ See Section V(D) for more information of the requirement of informed consent within the U.S.

⁵⁹ *Id.*

⁶⁰ For the criteria developed by the IOM see Committee on Assessing Genetic Risks, Institute of Medicine, *Assessing Genetic Risks: Implications for Health and Social Policy* 5 (Lori B. Andrews et al., eds. 1994) [hereinafter IOM Report].

⁶¹ *Id.*

⁶² *Id.* at 5.

⁶³ The U.S. Congress established the MCHB (originally the Children’s Bureau) in 1912. In 1935, they enacted Title V of the Social Security Act, authorizing the MCHB services programs and providing a foundation and structure for assuring the health of American mothers and children. This organization is a bureau of the Health Resources and Services Administration under the U.S. Department of Health and Human Services. See MCHB Home Page, <http://mchb.hrsa.gov/about/default.htm> (last visited Oct. 3, 2005).

⁶⁴ See AAP, *supra* note 33.

⁶⁵ *Id.*

While the criteria in general have evolved throughout the years, no set has emerged as the benchmark for all states to follow. As a result, there is a vast disparity in the number of disorders screened among the states,⁶⁶ and children receive anywhere from four to thirty tests based solely upon where they are born.⁶⁷

While there is no one list of criteria that is universally followed among the states, there are two criteria that resonate throughout. First, there should be full understanding of the disorder to allow for accurate testing and provide effective treatment for those found to have a positive test result. Second, the test should offer a benefit to the newborn. Because these two criteria permeate all the lists developed, one may conclude that every state relied upon them to some degree when developing their screening panels.⁶⁸

Today, the development of new technology capable of testing multiple disorders from a single drop of blood is threatening the criteria upon which these programs have relied. Testing with this technology allows healthcare providers to identify more disorders; but these disorders do not necessarily meet the criteria. A full understanding of the technology itself, including the potential it provides for newborn screening, is necessary to grasp the legal and political implications of this change.

III. MS/MS THREATENS THE SCREENING CRITERIA DUE TO ITS POTENTIAL TO SIGNIFICANTLY EXPAND THE SCREENING PANEL

MS/MS, one of the primary advances in technology influencing newborn screening,⁶⁹ has the potential to expand the screening panel by testing for more disorders with just one drop of blood.⁷⁰ This expansion threatens the criteria used in the United States by encouraging expansion prior to fulfillment of the criteria.

Scientists initially considered MS/MS for use in newborn screening based on its ability to rapidly screen a single drop of blood for multiple

⁶⁶ *Id.*

⁶⁷ Because of this disparity, many now advocate for a federal policy mandating the number of disorders included in newborn screening. *See generally*, McCabe et al., *supra* note 3.

⁶⁸ Throughout the remainder of this comment, I will refer to these as the “two criteria” for including a disorder on the screening panel.

⁶⁹ Donald H. Chace, Theodore A. Kalas & Edwin W. Naylor, *Use of Tandem Mass Spectrometry for Multianalyte Screening of Dried Blood Specimens from Newborns*, 49 *CLINICAL CHEMISTRY* 1797, 1799 (2003) [hereinafter Chace et al.].

⁷⁰ *See*, American College of Medical Genetics/American Society of Human Genetics Test and Technology Transfer Committee Working Group, *Tandem Mass Spectrometry in Newborn Screening*, 2 *GENETICS IN MEDICINE* 267 (2000) [hereinafter ACMG/ASHG Working Group]; H. Hannon et al., *Outcomes from Tandem Mass Spectrometry (MS/MS) Workshops in the United States and the Performance Evaluation of MS/MS Laboratories*, 34 *SOUTHEAST ASIAN J. TROP. MED. & PUB. HEALTH* 121, 121 (2003).

disorders.⁷¹ The screening consists of analyzing the quantity of amino acids⁷² and acylcarnitines⁷³ present in the blood spot taken from the newborn.⁷⁴ In the case of inherited metabolic diseases, specific enzymes that facilitate the breakdown of amino acids or the conversion of fat to energy simply do not function.⁷⁵ The compound accumulates in the blood and tissue and becomes a poison to the child rather than a normal substance.⁷⁶ MS/MS measures these compounds in order to determine if too much is present in the newborn's blood, an indication of whether the child's metabolic system is functioning properly.⁷⁷ If an abnormal amount is present, the screeners can determine what particular disorder the child may possess based upon which molecule is in excess.⁷⁸ In this way, healthcare workers use a single drop of blood to determine the health of a child with regard to multiple disorders.

Advocates rationalize the use of MS/MS for newborn screening in a number of ways. First, they point to the machine's capability to screen for thirty or more metabolic disorders from one drop of dried blood.⁷⁹ In this way, MS/MS significantly increases the potential of including more disorders in newborn screening programs.⁸⁰ For certain metabolic disorders in which a treatment is known, early detection can result in a significant improvement in the health of the child.⁸¹ Furthermore, advocates argue that even if the treatment for a certain disorder is unknown, identification will still benefit the patient and family.⁸² Parents gain peace of mind in knowing the existence of the disorder and are better able to plan for the future.⁸³

⁷¹ See AAP, *supra* note 33.

⁷² Donald H. Chace, *A Layperson's Guide to Tandem Mass Spectrometry in Newborn Screening*, at <http://www.savebabies.org/NBS/msms-chace.php> (last visited Oct. 31, 2005) (on file with Journal) [hereinafter Layperson's Guide] (amino acids are the "building blocks" of proteins).

⁷³ *Id.* (acylcarnitine exists when a carnitine, the "transportation system" for fats in and out the cell's mitochondria, is attached to a fat indicating that it is functioning properly).

⁷⁴ W. Harry Hannon & Scott D. Grosse, *Using Tandem Mass Spectrometry for Metabolic Disease Screening Among Newborns: A Report of a Work Group*, 50 MMWR 1 (2001).

⁷⁵ See Chace, *supra* note 69.

⁷⁶ See *id.*

⁷⁷ See Hannon & Grosse, *supra* note 74.

⁷⁸ See Chace, *supra* note 69.

⁷⁹ See, e.g., Press Release, Mayo Clinic, Mayo Clinic Researcher Calls for Improved Newborn Screening Minnesota Method Accurate, Cost-Effective (Feb. 21, 2005), available at <http://www.mayoclinic.org/news2005-rst/2683.html> (last visited Oct. 3, 2005) (the doctor interviewed pointed out that MS/MS is able to screen for "upwards of 40 ... genetic diseases").

⁸⁰ *Id.*

⁸¹ See Hannon & Grosse, *supra* note 74, at 2.

⁸² *Id.*

⁸³ See Ellen Wright Clayton, *Genetic Testing in Children*, 22 J. MED. & PHIL. 233, 238 (1997).

Additionally, scientists argue analysis by MS/MS is more sensitive,⁸⁴ specific, and reliable than previous methods of newborn screening.⁸⁵ For example, research has indicated that MS/MS has a false positive rate up to ten-fold lower for PKU screening than the best method previously available.⁸⁶ This device has also proven to be very accurate in that it can measure a very small amount of material for the presence of a single compound with excellent precision.⁸⁷ The performance rate for analysis is another rationale for its adoption in newborn screening, as the test takes only a matter of minutes from start to finish.⁸⁸ For these reasons, proponents of MS/MS argue that states should adopt it for use in their newborn screening programs.⁸⁹

While the above rationales present a compelling argument for incorporation of MS/MS into newborn screening programs, their evaluation is not possible without also considering the negative impact of such an adoption. One aspect of the technology advanced in opposition to its use for newborn screening is the cost.⁹⁰ The instrument itself costs around \$400,000 per machine, but this expense alone is far from the total necessary to incorporate the technology into screening programs.⁹¹ States must also consider the cost of counseling and treatment as they are also an integral part of the programs. In addition, scientists suggest that the use of MS/MS could increase the number of patients identified annually by fifty to one-hundred percent.⁹² These children will require follow-up testing, which can lead to expensive treatments and/or counseling for the affected family members.⁹³ This in turn will require an increase in physicians, nutritionists, and genetic counselors involved in newborn screening programs.⁹⁴ Furthermore, while the method of screening is itself simple, analyzing the results is not.⁹⁵

⁸⁴ Sensitivity of testing refers to the ability of a test to pick-up a set factor, such as the abundance of a particular amino acid in the blood. Specificity refers to the ability of the test to accurately report what amino acid it has detected.

⁸⁵ See, e.g., AAP, *supra* note 37; V. Wiley et al., *Newborn Screening – Is It Really That Simple?*, 34 SOUTHEAST ASIAN J. TROP. MED. & PUB. HEALTH 107, 107 (2003) (MS/MS has shown a sensitivity of 95.9% and specificity of 99.8%).

⁸⁶ See *id.*; see also ACMG/ASHG Working Group, *supra* note 70, at 267 (“MS/MS is more accurate than most methods now in use for newborn screening and would thus provide more specific and sensitive screening for [PKU]”).

⁸⁷ See Layperson’s Guide, *supra* note 72.

⁸⁸ See ACMG/ASHG Working Group, *supra* note 70, 267.

⁸⁹ *Id.*

⁹⁰ See Chace et al., *supra* note 69.

⁹¹ *Id.*

⁹² ACMG/ASHG Working Group, *supra* note 70, at 268.

⁹³ See Hannon & Grosse, *supra* note 74, at 14.

⁹⁴ *Id.*

⁹⁵ See Layperson’s Guide, *supra* note 72.

Accurate analysis of the data requires extensive training, which further adds to the expense of its incorporation.⁹⁶

In addition to cost, those who oppose adopting MS/MS for newborn screening cite the lack of knowledge about the disorders themselves.⁹⁷ For example, the specificity of the technology may lead to identification of carriers who will never become symptomatic due to differing degrees of severity within the disorder itself.⁹⁸ Full understanding of the disorder is necessary in order to differentiate between those who will suffer from it and those who merely carry the trait.⁹⁹ This issue leads many to caution against outright adoption of MS/MS into newborn screening programs until more knowledge is available about the disorders themselves.¹⁰⁰

Despite the above-mentioned drawbacks of incorporating MS/MS, thirty-four states¹⁰¹ have already incorporated it into their newborn screening programs.¹⁰² States rationalize this adoption by referring to the vast number of disorders MS/MS can detect.¹⁰³ In addition, advocacy groups have exerted significant pressure on policy-makers to adopt this technology,¹⁰⁴ undoubtedly affecting the incorporation of the technology in many states.¹⁰⁵ Due to the pressure from such interest groups, many states are expanding their panels to include disorders never before incorporated into newborn screening.¹⁰⁶

This technology and the resulting expansion of newborn screening is changing the face of newborn screening in the United States and worldwide. The increasing ability to detect disorders pushes the limits of already established criteria.¹⁰⁷ Questions remain as to whether the criteria should, or must, change due to the adoption of MS/MS.

⁹⁶ See ACMG/ASHG Working Group, *supra* note 70, at 268.

⁹⁷ See Wilcken et al., *supra* note 12, at 2304.

⁹⁸ See Hannon & Grosse, *supra* note 74, at 14.

⁹⁹ See Wilcken et al., *supra* note 12, at 2304.

¹⁰⁰ See, e.g., *supra* note 74, at 14.

¹⁰¹ Three of these states — California, Oklahoma, and Missouri — have mandated the screening but it is not yet implemented. NATIONAL NEWBORN SCREENING STATUS REPORT (Oct. 21, 2005), <http://genes-r-us.uthscsa.edu/nbsdisorders.pdf> (last visited Oct. 1, 2005).

¹⁰² *Id.*

¹⁰³ Chace et al., *supra* note 69.

¹⁰⁴ See Wilcken et al., *supra* note 12, at 2309.

¹⁰⁵ See *id.*

¹⁰⁶ In 1998, state mandatory panels screened from 0 to 8 disorders, while today, some states screen for more than 30, with North Dakota screening for a total of 38 disorders, 32 of which are screened using MS/MS. This startling increase indicates the effect MS/MS technology has had on the screening panel. *Id.*

¹⁰⁷ Brink, *supra* note 7 (Lainie Ross, Associate Professor of Pediatrics and Clinical Director of the MacLean Center of Clinical Medical Ethics at the University of Chicago stated, “[w]e may be creating this whole community of people who have a diagnosis, some of whom never get sick.”).

In addressing these issues, the United States can look to Australia, which expanded newborn screening through the use of MS/MS. A close evaluation of the results of the screening within that country is helpful in determining what, if any, steps the United States should take in this area.

IV. AUSTRALIA'S USE OF MS/MS FOR NEWBORN SCREENING REVEALS PROBLEMS IN SUCH APPLICATION OF THE TECHNOLOGY

An Australian study utilizing MS/MS for newborn screening sheds light on the problems associated with using this technology. Specifically, such screening will result in the false identification of those who will never be affected by a particular disorder.¹⁰⁸ In 1998, the New South Wales newborn screening program became the first to use MS/MS.¹⁰⁹ Over the next four years, the state laboratory tested 362,000 newborns for thirty-one inborn errors of metabolism using this technology.¹¹⁰ The screeners compared these results to the previous rate of clinical diagnosis for four preceding four-year periods.¹¹¹ At the end of the four years, screening had identified and diagnosed fifty-seven newborns — forty-eight through screening and six through clinical diagnoses occurring at or before the time the screening results were available.¹¹² Seven other patients received clinical diagnosis after the testing period.¹¹³ Two patients born to mothers with a known risk who also had affected siblings declined screening.¹¹⁴

In comparing the results to the prior history of clinical diagnoses for disorders within newborns, the researchers found that this screening diagnosed two disorders at a significantly higher rate:¹¹⁵ medium-chain and short-chain acyl-coenzyme A ("CoA") dehydrogenase deficiency.¹¹⁶ While there is no clear evidence whether identification of the short-chain variant will be clinically useful,¹¹⁷ identification of the medium-chain variant ("MCADD") may prevent death among infants.

¹⁰⁸ See Wilcken et al., *supra* note 12, at 2309.

¹⁰⁹ See Hannon & Grosse, *supra* note 74, at 33 (reporting on Bridget Wilcken & Veronica Wiley, Tandem Mass Spectrometry in the New South Wales Newborn Screening Program for Metabolic Disease Screening Among Newborns Workshop (June 2000)).

¹¹⁰ Wilcken et al., *supra* note 12, at 2308.

¹¹¹ *Id.* at 2308.

¹¹² *Id.* (the 6 that were identified clinically are also included in the 48 identified through the screening).

¹¹³ *Id.* at 2309.

¹¹⁴ *Id.* at 2309-10.

¹¹⁵ *Id.* at 2309.

¹¹⁶ *Id.*

¹¹⁷ *Id.* at 2309-11.

MCADD is a rare disease caused by the lack of an enzyme required to convert fat to energy.¹¹⁸ Exposure of a child with MCADD to a period of fasting can result in serious injuries or even death¹¹⁹ resulting from a build-up of fatty acids in the blood.¹²⁰ Scientists estimate that the first episode of fasting is fatal in thirty to fifty percent of patients.¹²¹ Treatment for this disorder requires avoiding these periods of fasting.¹²²

Following PKU, MCADD was the most commonly detected disorder in the Australian study.¹²³ The results of this study indicated the disorder has a prevalence of approximately one in 19,000.¹²⁴ However, many patients identified by the screening as having the disorder remained healthy.¹²⁵ This absence of symptoms accounts for the significant difference between children diagnosed through the MS/MS screening versus those diagnosed clinically in the period prior to the study.¹²⁶ The children who remained undiagnosed under the previous model appear to have a different form of the disease that either presents itself in a significantly milder fashion or perhaps is completely benign.¹²⁷ However, when MS/MS is used, there is no way to differentiate these patients from those who are indeed at risk.¹²⁸ For this reason, physicians must treat all patients receiving a positive diagnosis as if they are at risk, even though the child may develop symptoms.¹²⁹ The falsely identified children and their parents will be required to undergo

¹¹⁸ See Save the Babies Through Screening Foundation, Inc., *Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)*, at <http://www.savebabies.org/diseasedescriptions/mcadd.php> (last visited Oct. 4, 2005); Neil A. Holtzman, *Expanded Newborn Screening – How Good is the Evidence*, 290 JAMA 2606 (2003).

¹¹⁹ See Washington State Department of Health, *Newborn Screening: Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)*, available at <http://www.doh.wa.gov/EHSPHL/PHL/Newborn/mcadd.htm> (last visited Oct. 4, 2005).

¹²⁰ See Karl S. Roth, *Medium-Chain Acyl-CoA Dehydrogenase Deficiency*, in E-MEDICINE (Edward Kaye et al., eds. 2003), available at <http://www.emedicine.com/ped/topic1392.htm> (last visited Oct. 4, 2005).

¹²¹ ACMG/ASHG Working Group, *supra* note 70, at 2671.

¹²² See Department of Public Health for the State of Connecticut, *Genetics Newborn Screening Program: MCADD Family Fact Sheet* (Jan. 19, 2005), available at <http://www.dph.state.ct.us/BCH/NBS/Resources/mffs.pdf> (last visited Oct. 4, 2005).

¹²³ See Wilcken et al., *supra* note 12, at 2311; V. Wiley et al., *Newborn Screening with Tandem Mass Spectrometry: 12 Months' Experience in NSW Australia*, 88 ACTA PAEDIATRICA SUPPLEMENT 48 (1999).

¹²⁴ See Kevin Carpenter et al., *Evaluation of Newborn Screening for Medium Chain Acyl-CoA Dehydrogenase Deficiency in 275,000 Babies*, 85 ARCHIVE OF DISABLED CHILD FETAL NEONATAL EDUCATION F105 (2001).

¹²⁵ See Wilcken et al., *supra* note 12, at 2311.

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ BS Andresen, et al., *The Molecular Basis of Medium-chain Acyl-CoA Dehydrogenase (MCADD) Deficiency in Compound Heterozygous Patients: Is There Correlation Between Genotype and Phenotype*, 6 HUMAN MOLECULAR GENETICS 695 (1997).

¹²⁹ See Wilcken et al., *supra* note 12, at 2311.

genetic counseling and a stringent management plan in order to prevent a risk that was never a reality to the child.¹³⁰ The Australian scientists themselves acknowledged that “decisions on expansion of the newborn screening programmes to include [MCADD] deficiency should be taken in the knowledge that this is a complex disorder, and that not all cases discovered by newborn screening may be at risk.”¹³¹

This overly-broad treatment due to insufficient knowledge of a particular disorder is not a new development within newborn screening programs — it was also present in the early days of PKU screening.¹³² While the researchers during that time eventually gained enough information to lower the false-positive results, the interim period saw severe consequences for many children falsely identified as diseased.¹³³ The fact that a different disorder is encountering similar problems indicates that states should use caution before proceeding with such screening in order to avoid this result for even more disorders.

Despite the issues surrounding diagnosis of children at risk for MCADD, the New South Wales program successfully demonstrated that MS/MS detects more cases of inborn errors of metabolism than clinical diagnosis.¹³⁴ Like MCADD, however, many of the other thirty-one disorders included in the screening are complex and not yet fully understood. Therefore, not all infants receiving positive results will actually be at risk as some will never become symptomatic.¹³⁵ Until scientists conduct more studies of these disorders, this result is inevitable.¹³⁶

V. THE UNITED STATES SHOULD BE CAUTIOUS WHEN INCORPORATING MORE DISORDERS INTO THEIR SCREENING PANELS

The results of the Australian study indicate that the United States, and others considering the usage of MS/MS to expand newborn screening panels, should proceed cautiously prior to incorporating new disorders into their programs. In the United States, a direct comparison to the results of the Australian study is possible due to a close resemblance between the newborn screening programs of these two countries.

¹³⁰ See Carpenter, *supra* note 124, at F105.

¹³¹ *Id.* at F108.

¹³² Clayton, *supra* note 20, at 106.

¹³³ *Id.*

¹³⁴ Wilcken et al., *supra* note 12, at 2304.

¹³⁵ Carpenter et al., *supra* note 124, at F105.

¹³⁶ *Id.*

A. *Similarities Between the Australian and the United States' Newborn Screening Programs Provide for Accurate Comparisons of the Methods Used for Testing*

The United States can learn from the results of the Australian study due to similarities between the newborn screening programs in these two countries. Like the United States, Australia first established newborn screening programs in the late 1960s¹³⁷ and implemented them through state-wide programs around 1970.¹³⁸ Australia consists of six states and two territories,¹³⁹ each of which is responsible for coordinating newborn screening services through centralized state laboratories.¹⁴⁰ This resembles the state-by-state approach currently in use in the United States. In addition, the Australian program is fully publicly funded;¹⁴¹ much like its counterpart in the United States where each state's Department of Health provides most of the funding.¹⁴² One final similarity is the method both countries use for developing the screening panel. In Australia, a joint subcommittee of the Human Genetics Society of Australia ("HGSA") and the Division of Paediatrics of the Royal Australasian College of Physicians ("RACP") generates policy statements recommending screening policies applicable to all states and New Zealand.¹⁴³ The individual states then use these recommendations to determine the specifics of their program, including the methods used and disorders included in the screening panel.¹⁴⁴ In this way, the HGSA Policy Statements serve a similar function to the criteria developed by different advisory committees within the United States; they offer guidance to lawmakers in structuring the newborn screening programs.¹⁴⁵ Overall, the similarities between these two programs allow

¹³⁷ See HGSA Policy Statement 2004, *supra* note 18.

¹³⁸ Diane Webster, *Newborn Screening in Australia and New Zealand*, 34 SOUTHEAST ASIAN J. TROP. MED. & PUB. HEALTH 69, 69 (2003).

¹³⁹ The states are: New South Wales, Queensland, South Australia, Tasmania, Victoria, and Western Australia; the territories are: Australian Capital Territory and Northern Territory. See Australian Government: Department of Foreign Affairs and Trade, *Australia: An Introduction*, available at <http://www.dfat.gov.au/facts/intro.html> (last visited Oct. 4, 2005).

¹⁴⁰ HGSA Policy Statement 2004, *supra* note 18.

¹⁴¹ See Webster, *supra* note 138.

¹⁴² *Id.*

¹⁴³ *Id.*

¹⁴⁴ *Id.*

¹⁴⁵ In the most recent HGSA Policy Statement (2004), the committee listed the following criteria as factors that should be present for a disorder to be included within the newborn screening program: "(1) there is a benefit for the baby from early diagnosis (benefit to the family may also benefit the baby); (2) the benefit is reasonably balanced against financial and other costs; (3) there is a reliable test suitable for newborn screening; (4) there is a satisfactory system in operation to deal with diagnostic testing,

lawmakers in the United States to analyze the results of the Australian study when assessing the development of the programs within their state.

B. The Australian Study Demonstrates That Many of the Disorders Proposed for Addition into Newborn Screening in the United States Fail to Meet the Criteria Traditionally Relied Upon

When lawmakers in the United States assess their newborn screening programs in conjunction with the Australian study utilizing MS/MS, they will recognize that such technology is not appropriate for the screening of many disorders due to the failure of such disorders to meet the necessary criteria.¹⁴⁶ In many states, however, this expansion has already occurred or is in the process of occurring.¹⁴⁷ For these states, the issue is whether legislators need to make changes to the current programs in order to accommodate this expansion. An evaluation of these disorders using the two criteria discussed above indicates that care is necessary prior to their incorporation into the screening panel.

Now that scientists know MS/MS detects more disorders than previous screening methods,¹⁴⁸ the question is whether these new disorders meet the old criteria utilized by the states.¹⁴⁹ Closer evaluation reveals problems in this regard. One may argue that since these disorders have not previously been included in screening they must not meet the criteria. However, scientists rationalize the expansion of screening to include these

counseling, treatment and follow-up of patients identified by the test.” *Id.*; HGSA Policy Statement 2004, *supra* note 18.

¹⁴⁶ See *supra* Part II(B).

¹⁴⁷ See NATIONAL NEWBORN SCREENING STATUS REPORT (2005), *supra* note 101. Currently, only 11 states, including the District of Columbia, do not use this technology at all. It is mandated in 34 states (in 3 it has not yet been implemented), part of universal pilot programs in 4 states, and not mandated, but available through pilot programs or by request, in 7 states. Overlap occurs because in some states testing is mandated while in others it is available through pilot programs. For example, in New Jersey, 11 disorders are mandated while 8 are not mandated but available through pilot programs or by request. New Jersey is therefore included in both of these subgroups. *Id.*; see also P. Rinaldo, *Recent Developments and New Applications of Tandem Mass Spectrometry in Newborn Screening*, 16 CURRENT OPINION PEDIATRICS 427, 427 (2004) (“newborn screening in the United States is undergoing a rapid expansion driven by the introduction of tandem mass spectrometry in at least 34 state programs”); Alissa Johnson, *Newborn Genetic and Metabolic Disease Screening*, NATIONAL COUNCIL OF STATE LEGISLATURES (2005), available at <http://www.ncsl.org/programs/health/genetics/newborn.htm> (last visited Oct. 4, 2005) (“[r]ecent advances in technology have enabled some states to add a substantial number of conditions to the newborn screening panel in a relatively short timeframe”).

¹⁴⁸ See Wilcken et al., *supra* note 12, at 2304.

¹⁴⁹ For a list of disorders proposed for screening through MS/MS, see HGSA Policy Statement 2004, *supra* note 18, for Australia, and March of Dimes, *Recommended Newborn Screening Tests: 29 Disorders*, at http://www.marchofdimes.com/professionals/681_15455.asp (last visited Oct. 31, 2005) [hereinafter March of Dimes] for the U.S.

disorders by the increased rate of detection. The implications of such a change are apparent when evaluating one of these disorders in detail.

In the first Australian study on the usage of MS/MS for newborn screening, the researchers concluded that the greatest increase in the rate of diagnosis from the old system to the new one occurred with regard to MCADD.¹⁵⁰ A United States study in New England later reported similar results.¹⁵¹ This disorder is consequently one of the primary rationales for utilizing MS/MS in newborn screening. However, when compared against the current criteria for adding a disorder to the screening panels within the United States, it is clear that MCADD fails to meet the two required factors — knowledge of the disorder and benefit to the child.¹⁵²

First, scientists lack full understanding of this disorder. The significant increase noted in the Australian study of children identified with MCADD through MS/MS, versus those previously identified, indicates that at least some of these children have different genotypes for the disorder than those associated with severe health episodes or sudden death.¹⁵³ This increase is due to over-detection by the tandem mass spectrometer resulting from a lack of knowledge on the different genotypes associated with the disorder.¹⁵⁴ Instead of detecting only the children at severe risk, the screening picks up those with benign or mild forms of the disorder who will never develop symptoms.¹⁵⁵ More research is necessary to allow differentiation between these two groups. Until the genotype associated with the disorder is clearly understood, healthy children will continue to be labeled as diseased — a diagnosis which could potentially affect many aspects of their life.¹⁵⁶ The criteria require full understanding of a disorder prior to their incorporation in screening programs for precisely this reason.

¹⁵⁰ Wilcken et al., *supra* note 12, at 2308.

¹⁵¹ Waisbren et al., *supra* note 11, at 2567, 2570-71.

¹⁵² See *supra* Part II(B).

¹⁵³ See Peter T. Clayton et al., Screening for Medium Chain Acyl-CoA Dehydrogenase Deficiency Using Electrospray Ionization Tandem Mass Spectrometry, 79 ARCHIVES DISEASE CHILD 109 (1998); see also Waisbren et al., *supra* note 11, at 2570-71.

¹⁵⁴ Holtzman, *supra* note 118, at 2606 (the increase in rate of detection seems to be due to MS/MS overdetection because of failure to distinguish between infants at risk). See also Andresen et al., *supra* note 128, at 695 (the genotype/phenotype correlation in MCADD is not clear). Similar over-detection was discovered with Isovaleric Acidemia (IVA). MS/MS identified 19 subjects with a genetic mutation, and then found six healthy older siblings with identical genotype and biochemical evidence of IVA. These findings indicate there is a mild and potentially asymptomatic phenotype of IVA. Regina Ensenaer et al., *A Common Mutation is Associated with a Mild, Potentially Asymptomatic Phenotype in Patients with Isovaleric Acidemia Diagnosed by Newborn Screening*, 75 AM. J. HUM. GENETICS 1136, 1137 (2004).

¹⁵⁵ See generally Carpenter, *supra* note 124.

¹⁵⁶ Clayton, *supra* note 20, at 106-109 (suggesting that this mislabeling can cause disruption in the development of the parent-child relationship, and also may result in employment or insurance discrimination against the child.).

Second, there is no clear benefit to the child. The large number of children identified from screening who developed no symptoms indicates that the risk is not as high as was previously believed.¹⁵⁷ In reality, not all children with this genotype are at risk. Since they are not at risk, the testing is not beneficial to them. MCADD therefore fails with regard to this criterion.

Those advocating the use of MS/MS in newborn screening argue that this technology will allow for detection of additional disorders from a single screen.¹⁵⁸ MCADD is one of the strongest examples in this regard due to the fact research has shown MS/MS identifies more patients with this disorder.¹⁵⁹ However, the prior discussion demonstrates that such screening presents new issues not encountered in the previous screening programs based upon the failure of this disorder to meet the criteria currently used. If MCADD presents the best results, the other disorders proposed for adoption¹⁶⁰ will also fail to fit within these criteria.

1. Adapting Criteria to Incorporate More Disorders into Newborn Screening Programs Is Incongruent with Legal Principles of the United States

In light of differences in American legal principles, the United States must differ from Australia in the method used to allow for inclusion of new disorders within American states' screening programs. Australia has resolved the problems faced in the United States regarding the adoption of these new disorders through a slight modification to their criteria, but a similar change is not possible within the United States because of the differences between the criteria utilized by the two countries. While the United States requires full understanding of the disorder prior to incorporation in a screening panel, the HGSA Policy Statement does not include such a requirement.¹⁶¹ This absence avoids the issue encountered in the United States arising from the requirement for full understanding of the various genotypes of a disorder, such as MCADD, prior to adding it to the

¹⁵⁷ See Carpenter et al., *supra* note 124, at F1008 ("not all cases discovered by newborn screening may be at risk.").

¹⁵⁸ See Laypersons Guide, *supra* note 72.

¹⁵⁹ See Wilcken et al., *supra* note 12.

¹⁶⁰ Another example is 3-Methylcrotonyl-CoA carboxylase deficiency ("3MCC"), which is described as a disorder that can lead to brain damage, seizures, liver failure and death, or may result in no symptoms at all. Furthermore, while treatment *may* be helpful, a positive result on the screening test "could be related to abnormal metabolites in the mother and not the baby." March of Dimes, *supra* note 149.

¹⁶¹ HGSA Policy Statement 2004, *supra* note 18.

states' screening panels. The Australian states have not had to address this issue in adding MCADD, as well as other disorders, to its screening panels.

Additionally, Australian policy-makers have made slight but significant adjustments to their criteria in order to allow incorporation of such disorders into newborn screening. The first criterion in the 1999 HGSA Policy Statement asserts that "newborn screening is recommended provided that . . . [t]here is a benefit for the individual from early diagnosis."¹⁶² However, by 2004, this requirement changed to state: "[t]here is benefit for the baby from early diagnosis (*benefit to the family may also benefit the baby*)."¹⁶³ Rather than requiring a benefit to the child alone, Australia now allows for the addition of a disorder if it offers benefit to the family.¹⁶⁴ If the benefit need not be to the child alone, this implies that the child also need not be at risk, as is required in the United States. This change, however, allows for the addition of almost any genetic disorder to the newborn screening panel because the family of the child will likely benefit by acquiring knowledge regarding their own genetic make-up. For example, such knowledge can assist parents, and other relatives, in future decisions regarding child-bearing. Therefore, it is apparent that Australia has greatly expanded the scope of its newborn screening programs to incorporate numerous new disorders based upon this single change in the criteria.

2. *The United States Must Either Change Its Criteria or Limit the Usage of MS/MS*

If the American states intend to continue using MS/MS for newborn screening, there are two ways in which they can address the issue of new disorders that fail to meet the current criteria. First, the states could choose to keep the criteria and simply not allow incorporation of new disorders into the screening panel until they meet all of the necessary criteria. Second, the states may decide to change the criteria in order to incorporate these disorders at the present time, as was done in Australia.

¹⁶² HGSA Policy Statement 1999, *supra* note 16.

¹⁶³ HGSA Policy Statement 2004, *supra* note 18 (emphasis added).

¹⁶⁴ In an e-mail received from Ms. Diane Webster, chairperson of the HGSA-RACP Newborn Screening Committee, this change in wording was explained as follows: "It was clear that there was less worry to the family if the cause of the failing to thrive was known, and of course once the presence of an autosomal recessive disorder is known in a family they can make better informed reproductive choices and the committee wanted to word the policy so benefits of this type (not directly to the individual) could be validly considered." E-mail from Diane Webster, Chairperson of the Joint HGSA-RACP Newborn Screening Committee, to Lauren Fisher, Law Student, University of Washington School of Law (Apr. 27, 2005) (on file with Journal).

The second option is not viable for the United States. Australia amended its criteria to allow for testing of a child so long as it offers benefit to either the child or the child's family. This enables testing of one individual in order to benefit another. A similar change in the United States is contrary to American values in that it violates the principle of personal autonomy.¹⁶⁵ Therefore, such an amendment would not be legally acceptable in the United States.

The remaining option for the United States is to leave their system unaltered, thereby choosing not to expand the screening panel until a disorder fulfills the criteria. There are a number of problems associated with this option. First, and perhaps most importantly, one of the primary rationales for using MS/MS is its ability to screen for a large number of disorders from a single drop of blood.¹⁶⁶ Restricting such broad application of MS/MS reduces the value of an expensive piece of medical equipment. States must then decide whether to budget for MS/MS when previously used screening methods can already test for the approved disorders. Only the states themselves can make this determination through a cost-benefit analysis.

The second issue raised is whether the states will be able to refrain from adding disorders until they meet the criteria. Once this technology is in place, pressure from advocacy groups may lead state policy-makers to abandon the traditional criteria in order to add new disorders to the screening panel. In the past, advocacy groups have played a significant role in the expansion of newborn screening programs by lobbying for the inclusion of more genetic disorders within the screening panel.¹⁶⁷ In recent years, such lobbying has proved effective, and there is a significant trend in the states to increase the screening panel.¹⁶⁸ Therefore, it is not only safe to assume that the adoption of this technology will lead to an increase in the number of disorders tested; it is nearly a proven fact.¹⁶⁹ Even if states do not intend to

¹⁶⁵ See *Washington v. Glucksberg*, 521 U.S. 702, 777 (1997) (Souter, J., concurring) (there is a constitutionally protected liberty interest in bodily integrity and the right to determine what medical treatment shall be accepted or refused).

¹⁶⁶ Cf. ACMG/ASHG Working Group, *supra* note 70, at 267.

¹⁶⁷ See Holtzman, *supra* note 118; see also March of Dimes, *supra* note 149; Save Babies Through Screening Foundation Home Page, at <http://www.savebabies.org> (last visited Oct. 4, 2005) (Save the Babies is an organization formed by parents of disabled children and an influential advocacy group that has exerted pressure upon legislators to add more disorders to newborn screening).

¹⁶⁸ From 1998 to 2004, some U.S. states increased their screening panel from less than 5 to more than 30. This significant increase is due to the incorporation of MS/MS technology into these programs and shows the impact advocacy groups have over the legislative process in this area. NATIONAL NEWBORN SCREENING STATUS REPORT, *supra* note 101.

¹⁶⁹ For a complete list of all the disorders currently mandated by states for inclusion in the newborn screening program, see *id.*

expand the screening panel beyond those disorders meeting the criteria, such expansion may be inevitable.¹⁷⁰

Given that many states have already incorporated numerous new disorders into their newborn screening panels, states should not mandate this screening until the disorders meet the criteria previously required.¹⁷¹ For many disorders, such as MCADD, this requirement would mean increasing the knowledge of the disorder itself to raise the false-positive rate to an acceptable level. Some states have implemented pilot programs to gain this knowledge without mandating screening.¹⁷² However, this action also raises legal issues policy-makers must address before moving forward with such programs.

C. *The Informed Consent Requirements in the United States Restrict Expansion of Newborn Screening Through MS/MS*

The doctrine of informed consent further restricts expansion of newborn screening. Traditionally, every disorder included within screening caused a severe risk to the health of the child, as was required to meet the criteria. A severe health risk created a compelling reason to require the screening. However, by expanding the scope of the screening panel to include disorders not posing as great a threat, the use of MS/MS reduces the compelling nature of the need to screen.

Informed consent developed out of the 1946 Nuremberg Code¹⁷³ and has become one of the cornerstones of our healthcare system. This principle requires healthcare providers to receive voluntary and fully informed consent from a patient, or that patient's representative, prior to performing any treatment.¹⁷⁴ Newborn screening programs, however, have accompanied the emergence of an alternate method of consent different than full and voluntary consent of the parent or guardian. While all states currently have

¹⁷⁰ See William J. Rhead & Mira Irons, *The Call from the Newborn Screening Laboratory: Frustration in the Afternoon*, 51 PEDIATRIC CLIN. NORTH AM. 803, 804 (2004) (observes that some disorders have been added to newborn screening programs in the United States without researchers knowing if there is a true benefit to early diagnosis and treatment, which is one of the criteria traditionally used for including a disorder in the screening panel).

¹⁷¹ For states already mandating screening of disorders that do not meet the criteria, policy-makers should at least discuss the implications of such policy and make adjustments they deem appropriate.

¹⁷² See NATIONAL NEWBORN SCREENING STATUS REPORT, *supra* note 101 (Florida, Louisiana, Maryland, Massachusetts, Montana, Nebraska, New Jersey, Oregon, Pennsylvania, South Dakota, Texas and Utah currently use pilot programs in their newborn screening programs).

¹⁷³ See *Risk and Vulnerable Groups*, 4 ENCYCLOPEDIA OF BIOETHICS 2365, 2368 (3d ed., Stephen G. Post ed., 2005) ("[t]he voluntary consent of a human subject is absolutely essential").

¹⁷⁴ See, e.g., *Canterbury v. Spence*, 464 F.2d 772, 780 (D.C. Cir. 1972.) ("[t]rue consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowledgeably the options available and the risks attendant upon each.")

statutes requiring newborn screening,¹⁷⁵ only Wyoming¹⁷⁶ and Maryland¹⁷⁷ require informed consent by the parents prior to screening.¹⁷⁸ All others, with the exception of South Dakota,¹⁷⁹ have an “opt out” policy¹⁸⁰ under which parents must explicitly refuse screening in order to prevent it from occurring.¹⁸¹ In the majority of states, parents must base this refusal upon specific enumerated reasons, such as religion.¹⁸² However, many states deny parents the opportunity to “opt out.”¹⁸³ Research has indicated these states rarely present parents with an opportunity to refuse testing.¹⁸⁴ Instead, healthcare workers inform the parents about the testing only after it has occurred.¹⁸⁵

The justification for allowing states to perform newborn screening without the explicit informed consent of the parent is that parents do not have the authority to forego effective treatment for their child when that child has a life-threatening condition.¹⁸⁶ Since all of the disorders *traditionally* incorporated into the newborn screening panel were both life-threatening and amenable to treatment, the compelling interest of protecting the health of the child outweighed the infringement upon the fundamental right of the parent.¹⁸⁷ States now face the question of whether the current

¹⁷⁵ Cynthia E. Fruchtman & Francis C.J. Pizzulli, *Ethical Aspects of Genetic Testing*, 20 WHITTIER L. REV. 411, 415 (1998).

¹⁷⁶ WYO. STAT. ANN. § 35-4-801(c) (1977) (“Informed consent of parents *shall* be obtained”) (emphasis added).

¹⁷⁷ MD. CODE ANN., [Health] § 13-109(e)(2) (1982).

¹⁷⁸ See AAP Policy Statement, *supra* note 23. See also, Elaine H. Hiller et al., Public Participation in Medical Policy Making and the Status of Consumer Autonomy: The Example of Newborn Screening in the United States, 87 AM. J. PUB. HEALTH 1280, 1283 (1997).

¹⁷⁹ S.D. CODIFIED LAWS § 34-24-17 (1973).

¹⁸⁰ For an example of legislation setting forth an “opt out” policy, see Washington’s applicable legislation at WASH. REV. CODE § 70.83.020.

¹⁸¹ See American Academy of Pediatrics: Committee on Bioethics, Policy Statement: *Ethical Issues with Genetic Testing in Pediatrics*, 107 PEDIATRICS 1451 (2001), available at <http://www.aap.org/policy/re9924.html> (last visited Oct. 5, 2005) [hereinafter AAP Policy Statement].

¹⁸² See Katherine L. Acuff, *Prenatal and Newborn Screening: State Legislative Approaches and Current Practice Standard*, in AIDS, WOMEN AND THE NEXT GENERATION – TOWARDS A MORALLY ACCEPTABLE PUBLIC POLICY FOR HIV TESTING OF PREGNANT WOMEN AND NEWBORNS 121, 134-162 (Ruth R. Faden et al., eds., Oxford University Press 1991) (listing screening statutes and their applicable opt out requirements).

¹⁸³ See Fruchtman & Pizzulli, *supra* note 175, at 416.

¹⁸⁴ *Id.*

¹⁸⁵ See *id.*

¹⁸⁶ See AAP Policy Statement, *supra* note 181; George C. Cunningham, *Balancing the Individual’s Right to Privacy Against the Need for Information to Protect and Advance Public Health*, in GENETIC SCREENING FROM NEWBORNS TO DNA TYPING 210 (Bartha Maria Knoppers & Claude M. Laberge eds., 1990).

¹⁸⁷ See, e.g., *Parham v. J.R.*, 442 U.S. 584, 602 (1979) (parents have a constitutionally protected right to obtain needed medical treatment for their child).

“opt out” method should, or must, change as they begin using MS/MS to screen newborns.

Australia serves as an example of how to implement informed consent within these programs. Section 4.1 of the HGSA Policy Statement of 2004 states: “[p]arents should be informed of the availability of testing. If after discussion the parents refuse to have their newborn tested, they should sign a statement that they are fully informed about the test and the consequence of not testing.”¹⁸⁸ The committee amended this provision from the 1999 version which provided that “[t]he individual responsible should ensure that parents are given information about the screening prior to the test being taken.”¹⁸⁹ This amendment indicates that Australia tightened its informed consent requirements due to the incorporation of MS/MS into the programs. Instead of a parent merely needing to receive information about the screening, states now guarantee a full discussion regarding the screening program’s affect on their child. The use of MS/MS has therefore led to a more meaningful consent requirement in Australia.

In the United States, a similar change is necessary based on the incorporation of this technology. While the current opt out policy was justifiable with regard to the traditional disorders, the addition of new disorders to the screening panel removes the compelling nature of the testing for at least some of the disorders. Due to the current lack of understanding surrounding these new disorders, physicians can no longer assume that the children identified are in a life-threatening position. Therefore, the state interest no longer outweighs the fundamental right of the parents, because it lacks the compelling nature required. States should therefore mandate some form of consent for this testing to satisfy the legal requirements of the American healthcare system.¹⁹⁰

For the United States, merely requiring informed consent does not completely address the legal problems implicated by this new program. In order to learn more about these disorders, screening must occur on a large number of children to identify those affected. In fact, four states have already incorporated universal pilot programs on all newborns.¹⁹¹ Gaining the requisite information regarding the disorders will depend upon such pilot programs because otherwise, the sample population will not be large enough

¹⁸⁸ HGSA Policy Statement 2004, *supra* note 18.

¹⁸⁹ HGSA Policy Statement 1999, *supra* note 16.

¹⁹⁰ See *Canterbury v. Spence*, 464 F.2d 772 (D.C. Cir. 1972); *Truman v. Thomas*, 611 P.2d 902 (Cal. 1980).

¹⁹¹ NATIONAL NEWBORN SCREENING STATUS REPORT, *supra* note 101 (the 4 states are Louisiana, Maine, Massachusetts, and Oregon).

to produce any viable results. Therefore, states will need to implement universal pilot programs in order to identify subjects to study with the hope of increasing knowledge of the disorder itself. These universal pilot programs are more likely to be characterized as research programs rather than medical procedures.

D. Newborn Screening Pilot Programs May Potentially Be Classified As Research Which Further Prevents Expansion of the Screening Panel

One final hurdle facing the expansion of the screening panel after adoption of MS/MS is the possibility that such programs will be classified as research. Increased understanding of many of the disorders proposed for screening is required for the disorders to meet the criteria utilized by the states' lawmakers. Because they are so rare, scientists cannot effectively study these disorders unless screening occurs on an extremely large number of individuals.¹⁹² For this reason, many advocates of the technology have recommended implementing universal pilot programs¹⁹³ in order to utilize the technology to identify affected children, thus allowing further study on the disorder itself.¹⁹⁴ As was previously mentioned, four states currently practice universal screening¹⁹⁵ on all babies under pilot programs designed to study these rare disorders.¹⁹⁶ Such programs raise the issue of whether policy-makers should require specific informed consent from parents for this type of testing and whether the consent of the parent is sufficient.

The United States' scientific community defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."¹⁹⁷ Universal pilot programs potentially meet this definition. In the United States, however, there is a separate set of requirements for

¹⁹² The incidence rates of some of these disorders are: Citrullinemia – less than 1 in 100,000, Argininosuccinic academia – less than 1 in 100,000, Tyrosinemia type I – less than 1 in 100,000, Maple syrup urine disease – less than 1 in 100,000, isovaleric academia – less than 1 in 100,000. See March of Dimes, *supra* note 149.

¹⁹³ Australia also recommends such pilot programs. Section 5.2 of the 2004 HGSA Policy Statement provides that "[p]ilot studies should be undertaken to demonstrate the safety, effectiveness, validity and clinical utility of tests for additional disorders and new testing technologies." See HGSA Policy Statement 2004, *supra* note 18.

¹⁹⁴ See, e.g., HGSA Policy Statement 2004, *supra* note 18, at 3 ("Pilot studies should be undertaken to demonstrate the safety, effectiveness, validity and clinical utility of tests for additional disorders and new testing technologies.").

¹⁹⁵ I have used the term "universal pilot program" to refer to a pilot program testing the entire population of newborns within a state, thus making it universal.

¹⁹⁶ See National Newborn Screening Report, *supra* note 191.

¹⁹⁷ 45 C.F.R. § 46.102(d) (1991).

research programs,¹⁹⁸ and any research performed using federal funds,¹⁹⁹ or otherwise subject to federal regulation, must comply with 45 C.F.R. § 46.²⁰⁰ Section 46.117 of this regulation addresses the issue of informed consent and requires every research subject to give fully informed and voluntary consent to the procedure prior to testing.²⁰¹ However, the regulations provide additional protections for research with children.²⁰² If research poses only a minimal risk²⁰³ or offers direct benefit to the child, the consent of only one parent is required.²⁰⁴ Otherwise, the research requires the consent of both parents, unless the child has only one parent or legal guardian.²⁰⁵ Under either situation, the informed consent of *at least* one parent is required prior to testing.

E. Allowing Parents to Consent on Behalf of Their Children for Expanded Newborn Screening Does Not Satisfy the Informed Consent Requirements of the United States

The heightened requirements for research on children within the United States prevents parents from being required to consent before screening of disorders such as MCADD. Despite the allowance for testing with parental consent under 45 C.F.R. § 46, the Maryland case of *Grimes v. Kennedy Krieger Institute, Inc.*²⁰⁶ provides a strong argument against allowing a requirement for such consent in the current situation. This case held that parents cannot legally consent to the participation of their children in non-therapeutic research (research posing no potential benefit to the

¹⁹⁸ See Angela R. Holder, *Physician's Failure to Obtain Informed Consent to Innovative Practice or Medical Research*, 15 AM. JUR. PROOF OF FACTS 2d 711 § 3 (2005) ("After Nuremberg, and particularly in the early 1970's, public outcry over obvious abuses of research subjects, some of whom did not even know that they were research subjects, led to several congressional investigations and consequent strict regulation, particularly as to the informed consent of the research subject in all federally-funded research activities, or those carried out in federal institutions.").

¹⁹⁹ Federal funds provide primary funding for newborn screening programs in the U.S., thus placing these programs under the provisions of 45 C.F.R. § 46 (1991).

²⁰⁰ 45 C.F.R. § 46.101 (1991).

²⁰¹ 45 C.F.R. § 46.116 (1991) (general requirements for informed consent state that "[e]xcept as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative...").

²⁰² 45 C.F.R. § 46, Subpart D (1991).

²⁰³ "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 C.F.R. 46.102(i).

²⁰⁴ 45 C.F.R. § 46.408(b).

²⁰⁵ *Id.*

²⁰⁶ 782 A.2d 807 (Md. 2001).

child).²⁰⁷ The court stated that a parent “cannot consent to the participation of a child ... in non-therapeutic research or studies in which there is any risk of injury or damage to the health of the subject.”²⁰⁸ In reaching this decision, the *Grimes* court relied upon a decision from the New York Court of Appeals.²⁰⁹ In *T.D. v. New York Office of Mental Health*,²¹⁰ the Appellate Court determined that provisions in the regulations authorizing parents to consent on behalf of children for participation in non-therapeutic research posing greater than minimal risk to the child were insufficient.²¹¹ The *Grimes* court concurred with this conclusion in reaching its own holding. The decision in *Grimes* “sent shockwaves through the public health research community” due to its potential impact upon pediatric research.²¹² This impact clearly affects newborn screening, and state lawmakers should consider this legal precedent when deciding whether to utilize pilot programs in this area.

Based upon the *Grimes* holding, treatment for each disorder proposed for addition into the newborn screening panel through pilot programs should first be required to offer a therapeutic benefit to the child. Policy-makers should use a case-by-case analysis in making this determination. If no therapeutic benefit is present, then testing may not involve a potential risk to the child as is required for incorporation of the disorder into screening.

The pilot programs that states are using to study new disorders may be characterized as non-therapeutic research upon the child. These programs provide no significant potential benefit to the child due to the rarity of the disorders and the lack of knowledge on the disorder itself. Policy-makers cannot realistically view these disorders as providing a viable potential benefit to the child because they are incredibly rare.²¹³ Furthermore, even if a child receives a positive result, MCADD has shown there may continue to be no benefit to that child because it is unknown whether they will ever become symptomatic. Therefore, it is a stretch to say that a child is

²⁰⁷ *Id.* at 857-858.

²⁰⁸ *Id.* at 858.

²⁰⁹ *Id.* at 858.

²¹⁰ 650 N.Y.S.2d 173 (N.Y. App. Div. 1996).

²¹¹ *Id.* at 191.

²¹² Anna C. Mastroianni & Jeffrey P. Kahn, *Risk and Responsibility: Ethics, Grimes v. Kennedy Krieger, and Public Health Research Involving Children*, 92 AM. J. PUB. HEALTH 1073, 1073 (2002); See also Efi Rubinstein, *Going Beyond Parents and Institutional Review Boards in Protecting Children Involved in Nontherapeutic Research*, 33 GOLDEN GATE U. L. REV. 251, 290 (2003) (suggesting that parents are not in the position to make decisions for their children due to potential conflicts of interests and recommending developing child advocacy programs for non-therapeutic research.)

²¹³ For example, the average incidence rate for the 29 disorders recommended for screening by the March of Dimes is around 1 in 100,000. For specific incidence rates, see March of Dimes, *supra* note 149.

receiving a benefit from the addition of these disorders onto the screening panel due to the odds of that particular child actually receiving any type of benefit.

Under the *Grimes* ruling, since these programs offer no therapeutic benefit to the child, if they pose any risk to the child's health the consent of the parent is insufficient. The risk of discrimination, as well as potential physical and mental health problems resulting from the screening, are sufficient to negate the consent of the parent to this screening.

The risks presented to the physical health of the newborn from receiving this screening range from minimal to life-threatening. As was indicated through the hasty adoption of universal PKU screening, the treatment given to children with false positive test results can be severely debilitating, if not fatal.²¹⁴ The presence of this risk alone is sufficient to conclude that this screening does not satisfy the *Grimes* standard.

The potential negative impact of treatment, however, is not the only risk associated with such screening. A positive test result can adversely affect the parent-child relationship by interrupting the first days of the newborn's life when bonding is the most important.²¹⁵ In this way, screening poses a risk to the mental health of the children involved.

Another risk that arises is the potential for discrimination.²¹⁶ In the early stages of any screening program, mislabeling will undoubtedly occur.²¹⁷ Research has suggested that a positive test result can negatively affect the mental health of the child due to loss of self-esteem from being labeled as "diseased."²¹⁸ Children labeled as "diseased" forever carry the burden of such a designation, even if they never present symptoms. This labeling can result in discrimination against the child, and perhaps even against the family. In 1998, studies indicated that there had been approximately 200 documented cases of discrimination by insurance companies against healthy individuals based upon the presence of a genetic

²¹⁴ See Clayton, *supra* note 20, at 109.

²¹⁵ See L.N. Al-Jader et al., *Attitudes of Parents of Cystic Fibrosis Children Towards Neonatal Screening and Antenatal Diagnosis*, 38 CLINICAL GENETICS 460, 460 n.114 (1990) (voicing concerns about the effect that a diagnosis has on the parent-child relationship).

²¹⁶ TED PETERS, GENETICS AND GENETHICS: ARE WE PLAYING GOD? (1997) ("Even with a government regulated program of access to basic health services, the need to purchase supplemental insurance to cover serious diseases makes many of us with certain genetic configurations vulnerable to discrimination.").

²¹⁷ *Id.* at 105.

²¹⁸ The American Society of Human Genetics Board of Directors and The American College of Medical Genetics Board of Directors, *Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents*, 57 AM. J. HUMAN GENETICS 1233, 1238 (1995).

characteristic or trait revealed through genetic testing.²¹⁹ Falsely labeled children are therefore at potential risk of never qualifying for adequate health insurance based upon a test given to them when they were just a few days old. Families may also suffer a similar fate, as parents may be unable to obtain health insurance for their families based upon the knowledge of a genetic disorder within the family genome.²²⁰

These potential risks, along with available legal precedent on parental consent to research, lead to the conclusion that policy-makers cannot easily solve the issues surrounding informed consent for the use of MS/MS in newborn screening. Unlike Australia, simply requiring parents to provide such consent will not eliminate the potential legal problems implicated by such screening within the United States. The issues surrounding informed consent should therefore serve to restrict the use of this technology to disorders fitting within the two criteria. States should not include a disorder until it can fulfill these criteria, and screening of the child should not occur merely for the purpose of increasing knowledge of a particular disorder. The fact that screening newborns is easier for the researchers due to the large pool of subjects available does not justify overstepping the rights of even a single child.

F. Even If These Programs Are Classified As “Program Evaluation” Instead of Research, They Continue to Require Meaningful Consent from the Parents

One final alternative for policy-makers is to justify MS/MS newborn screening as “program evaluation.” The Center for Disease Control (“CDC”) has defined “program” to include any organized action such as a research project²²¹ and “evaluation” as the systematic application of scientific methods to assess the design, implementation, improvement or outcomes of a program.²²² These evaluations are conducted in order to discern whether programs should be “continued, improved, expanded, or curtailed [and] to assess the utility of new programs and initiatives.”²²³ The CDC temporarily excuses programs fitting within this definition from the requirements of 45 C.F.R. 46. Despite qualifying as research, the use of

²¹⁹ Fruchtmann & Pizzulli, *supra* note 178, at 413.

²²⁰ See Clayton, *supra* note 20, at 135.

²²¹ Center for Disease Control and Prevention, *Framework for Program Evaluation in Public Health*, 48 MMWR 1, 311 (1999).

²²² See Peter H. Rossi & Howard E. Freeman, *Evaluation: A Systematic Approach* 5-9 (5th ed., 1993).

²²³ *Id.* at 2.

MS/MS in newborn screening may be justified under this category. If this is the case, policy-makers may find that the research is acceptable despite its failure to satisfy the legal precedent's requirements for research upon children.

Even if these programs are justified under the definition of "program evaluation," there continues to be a need to at least require meaningful informed consent from the parent or guardian of the child screened. While parental consent is not sufficient if the program is viewed as research,²²⁴ this specialized categorization of research does not justify returning to the "opt out" policy currently in use.²²⁵ Again, many of the disorders added to the screening panel do not fulfill the criteria for screening and therefore do not present a compelling rationale to deprive the fundamental rights of the parents. Therefore, even if policy-makers categorize the use of MS/MS for newborn screening as "program evaluation," they should at the least amend the informed consent policies to require more meaningful consent of the parents.

VI. CONCLUSION

Overall, while many states are already utilizing MS/MS to screen for up to thirty-two inborn errors of metabolism,²²⁶ this analysis indicates that more caution is necessary in the future before continuing down this path. The capability of the technology should not outweigh reason when incorporating new disorders into screening programs. While the adoption of MS/MS into the Australian newborn screening programs was successful, differences in the informed consent of the United States requirements prevent it from following an identical path. State policy-makers must address informed consent and should amend the current policy to require more meaningful consent from the parent or guardian. These policy-makers should also consider how to address the criteria designed to give guidance when incorporating new disorders into the screening panel. If they choose to continue to rely upon these criteria, these policy-makers should use care not to expand screening for disorders failing to fulfill these criteria. Both of these recommendations will require caution by the states. Only by using caution can the United States avoid the problems experienced in the early days of PKU screening. Policy-makers should therefore use care to ensure

²²⁴ See *supra* Section V(D)(i).

²²⁵ See *supra* Section V(C).

²²⁶ North Dakota mandates screening all newborns for 32 disorders through MS/MS technology. NATIONAL NEWBORN SCREENING STATUS REPORT, *supra* note 101.

that the disorders included within their states' screening panel are sufficiently understood to prevent a similar result. The rights of the newborn child must remain at the forefront throughout all of these discussions. Such consideration will limit screening to situations where the test is beneficial to the child. In this way, technology can exist harmoniously with the deeply-rooted principles of the American legal system.